Overview of inherited zinc deficiency in infants and children

AUTHOR(S):

Kambe, Taiho; Fukue, Kazuhisa; Ishida, Riko; Miyazaki, Shiho

CITATION:

Kambe, Taiho ...[et al]. Overview of inherited zinc deficiency in infants and children. Journal of Nutritional Science and Vitaminology 2015, 61: S44-S46

ISSUE DATE:

2015-11-24

URL:

http://hdl.handle.net/2433/228379

Session Theme: Recent Topics in Infant Nutrition

Overview of inherited zinc deficiency in infants and children

Taiho Kambe, Kazuhisa Fukue, Riko Ishida, Shiho Miyazaki
Division of Integrated Life Science, Graduate School of Biostudies, Kyoto University, Kyoto 606-8502, Japan

The number of figures: 1

The number of tables: 1

Running Head: Inherited zinc deficiency in infants and children

*To whom correspondence should be addressed:
Taiho Kambe
Division of Integrated Life Science, Graduate School of Biostudies,
Kyoto University, Kitashirakawa-Oiwake-cho, Sakyo-ku, Kyoto 606-8502, Japan
Tel.: +81-75-753-6273
Fax: +81-75-753-6274
E-mail: kambe1@kais.kyoto-u.ac.jp

Summary

Zinc nutrition is of special practical importance in infants and children. Poor zinc absorption causes zinc deficiency, which leads to a broad range of consequences such as alopecia, diarrhea, skin lesions, taste disorders, loss of appetite, impaired immune function and neuropsychiatric changes and growth retardation, thus potentially threatening life in infants and children. In addition to dietary zinc deficiency, inherited zinc deficiency, which rarely occurs, is usually found during the infant stage and early childhood. Recent molecular genetic studies have identified responsible genes for two inherited zinc deficiency disorders, acrodermatitis enteropathica (AE) and transient neonatal zinc deficiency (TNZD), clarifying the pathological mechanisms. Both of these zinc deficiencies are caused by mutations of zinc transporters, although the mechanisms are completely different. AE is an autosomal recessive disorder caused by mutations of the *ZIP4* gene, consequently resulting in defective absorption of zinc in the small intestine. In contrast, TNZD is a disorder caused by mutations of the *ZnT2* gene, which results in low zinc breast milk in the mother, consequently causing zinc deficiency in the breast-fed infant. In both cases, zinc deficiency symptoms are ameliorated by a daily oral zinc supplementation for the patients. Zinc is definitely one of the key factors for the healthy growth of infants and children, and thus zinc nutrition should receive much attention.

Key words: zinc deficiency, infants, children, acrodermatitis enteropathica, transient neonatal zinc deficiency

神戸大朋、福江和久、石田理湖、宮﨑志保

京都大学大学院生命科学研究科

〒606-8502 京都市左京区北白川追分町
TEL: +81-75-753-6273, FAX: +81-75-753-6274

E-mail: kambe1@kais.kyoto-u.ac.jp

要約

亜鉛は生体内で多岐にわたる生理的役割を担うため、乳幼児の発育に極めて重要である。日々著しく成長する乳幼児における亜鉛の不足は、下痢、脱毛、皮膚炎、味覚障害、免疫機能や神経機能の低下、成長障害を引き起こすことが知られており、重篤な場合には生存を脅かすこともある。亜鉛欠乏は、遺伝により生じることもあり、最近の分子遺伝学的研究から２つのタイプの遺伝性亜鉛欠乏症の存在が明らかにされてきた。一つは、腸性肢端皮膚炎（AE）であり、消化管からの亜鉛吸収が障害されるために乳幼児が重篤な亜鉛欠乏を発症する。AEの原因遺伝子として亜鉛トランスポーターZIP4が同定されている。もう一つは、一過性新生児亜鉛欠乏症であり、乳児の亜鉛吸収能は正常であるが、母親が低亜鉛母乳を分泌したために乳児が亜鉛欠乏に陥る症例である。低亜鉛母乳を分泌する母親は、亜鉛トランスポーターZnT2に変異が見出されている。どちらの亜鉛欠乏においても、亜鉛を経口投与することで、その症状は改善する。これら亜鉛代謝に関わる分子を原因とする遺伝性亜鉛欠乏症の存在からも、乳幼児の健全な発育のための亜鉛の重要性は明白であり、乳幼児期における亜鉛栄養には、さらなる注意を払う必要がある。

Introduction

The optimal growth and development of infants and children requires a number of micronutrients. Zinc is one such micronutrient because it plays a pivotal role as a structural, catalytic, and signalling component within protein functions. Recent human proteomic analyses indicate that about 10% of proteins have been estimated to have the potential to bind zinc, which also reflects the indispensability of zinc for numerous physiological processes. In fact, zinc is essential for growth and development, immune, nervous system and endocrinal functions, and, in particular, is required during the first years of the life when the body is growing rapidly. Hence, in developing countries, where malnutrition is common, zinc deficiency is still a health problem; zinc deficiency increases the risk of morbidity and mortality of young children (1,2). In these countries, zinc supplementation in infants and children can prevent and reduce the severity of common diseases such as diarrhea, lower respiratory tract infections (3), and improve linear growth velocity. In developed countries, zinc deficiency in infants and children is much less common.

Zinc deficiency in infants and children usually occurs through insufficient intake of dietary zinc, but it also rarely occurs in an inherited manner, which is diagnosed as acrodermatitis enteropathica (AE) or transient neonatal zinc deficiency (TNZD) (4). Recent genetic studies have indicated that these conditions can be caused by mutations in zinc transporter genes and have clarified the pathological mechanisms in patients. This paper reviews current knowledge of zinc deficiency in infants and children, emphasizing the molecular basis of hereditary zinc deficiency disorders, AE and TNZD, from the standpoint of functions of the responsible zinc transporters.

Requirement of zinc for optimal growth of infants and children

Zinc in breast milk is bound to a number of different components including casein (14%), albumin (28%), low-molecular weight ligands (29%) and fat (29%) (5). Breast milk zinc concentrations, particularly in the first 3 months, are considerably higher than those of the maternal serum, which reflects the infant's requirement of a large amount of zinc for growth and development. Compared with full-term infants, preterm infants are in negative zinc balance at birth because of the lower capacity for gut absorption (6), and thus the demand for zinc increases rapidly in thriving preterm infants (7). Hence, the preterm infant has an increased risk of zinc deficiency compared

with a full-term infant, and symptomatic zinc deficiency has been mostly found in breast-fed preterm infants (8,9). Zinc deficiency also rarely occurs in breast-fed, full-term infants, in which hereditary AE and TNZD are likely (see below).

Children also need large amounts of zinc for their rapid growth. Recommendations for zinc intake differ between males and females at the age of 15 years in most countries, but range from 2.9 to 10.0 mg/day in children aged 5 years, 5.7–15.5 mg/day (boys) and 4.6–15.0 mg/day (girls) in children aged 10–15 years (3,10), which can enable severe zinc deficiency to be much less common in developed countries. Conversely, zinc deficiency in children is a health problem in developing countries, where the dietary needs of zinc may not be met. It is estimated that 4% of the global morbidity and mortality of young children between 6 months and 5 years of age are attributable to zinc deficiency (1,2).

Two zinc transporters, ZnT and ZIP

Zinc balance is primarily maintained through a regulated rate of intestinal absorption, and gastrointestinal secretion, renal excretion and sloughing of mucosal cells and integuments. After absorption, zinc is delivered to the peripheral tissues and cells, and then is distributed to the cellular compartments (11). In these processes, zinc transporters play crucial roles. In general, zinc transporters are divided into two groups, solute carrier 30A (SLC30A) and SLC39A; SLC30A is named Zn transporter (ZnT) and SLC39A is named Zrt, Irt-like protein (ZIP) (11,12). ZnT transporters export cytosolic zinc into the extracellular space or lumens of intracellular compartments, while ZIP transporters import zinc into the cytosol from the extracellular space or lumens of intracellular compartments. Most ZnT transporters have six putative transmembrane domains (TMDs), while ZIP transporters are thought to have eight TMDs. Both transporters are thought to capture zinc transport activity by forming complexes (dimers), although there have been no data for the x-ray crystal structure of ZnT and ZIP transporters. However, the bacterial ZnT homolog has been x-ray crystalized (13). Most ZIP transporters have been shown to be localized in the plasma membrane, while most ZnT transporters are localized in the intracellular compartments, and thus are functional to mobilize zinc into the lumens. Zinc transporters have crucial functions in physiology and dysfunctions of these result in inherited diseases. Thus far, four

inherited diseases caused by mutations of ZnT and ZIP transporters have been shown, and single nucleotide polymorphisms (SNPs) in both transporters related to pathologies of the diseases have been identified (4). Thus, the study of these zinc transporters is currently of great clinical interest. In zinc deficiency in infants and children, AE (MIM No. 201100) and TNZD (MIM No. 608118) have been shown to be caused by mutations of ZIP and ZnT transporter genes ZIP4 and ZnT2, respectively (Table 1). In both cases, symptoms of zinc deficiency, including erythematous and erosive dermatitis, persistent diarrhea, hair loss, and transient growth retardation, are ameliorated by zinc supplementation.

Acrodermatitis enteropathica and ZIP4 (SLC39A4)

AE is an autosomal recessive disorder caused by mutations of the *ZIP4/SLC39A4* gene (14), consequently resulting in reduced intestinal zinc absorption. AE is characterized by eczematous dermatitis, alopecia and diarrhea, typically occurring in early infancy but also after weaning in breast-fed infants (14), with an estimated frequency of about 1 in 500,000 (15). The zinc deficiency symptoms in patients with AE disappear if daily oral zinc supplementation is administered (1–3 mg/kg/day of elemental zinc) (15). At present, a myriad of mutations, including missense, nonsense, deletion, insertion, or splice-site mutations in the *ZIP4/SLC39A4* gene have been identified in AE patients (4) since the first reports of the mutations in 2002 (16,17). Pathogenic mutations in AE have been shown to result in defects in zinc responsive trafficking to the plasma membrane, reduced zinc uptake activity (18), or defects in processing, in which the extracellular amino-terminal domain of ZIP4 undergoes proteolytic cleavage during extended periods of zinc deficiency (19). The molecular mechanism causing severe dermatitis, which is one of the primary features in AE patients and severe zinc deficiency, have been shown not to be attributed to allergic contact dermatitis, but irritant contact dermatitis, which is caused by loss of Langerhans cells with a protective role against ATP-mediated inflammatory signals (20). However, those causing alopecia and diarrhea in AE patients remain unknown.

Transient neonatal zinc deficiency and ZnT2 (SLC30A2)

Zinc deficiency also occurs in breast-fed, full-term infants, which is caused by low zinc concentrations in the mother's breast milk. This type of zinc deficiency is called TNZD because zinc deficient symptoms only develop during breast-feeding and do not reoccur after weaning. In cases of TNZD, levels of zinc in the milk have been reported to be reduced by 75–90% compared with normal levels (21-24), which probably defines the onset and course of each patient. The low zinc levels in breast milk that result in TNZD are caused by mutations of the *ZnT2/SLC30A2* gene in mothers, who secret low zinc in their breast milk. Symptoms of TNZD are alleviated with zinc supplementation to the infant, but not to the mother. A number of missense mutations and a nonsense mutation of the *ZnT2/SLC30A2* gene have been identified. Missense mutations have been shown to cause aggresomal accumulation, lack of zinc transport activity or marked destabilization in ZnT2 protein (21-24). TNZD likely often occurs in an autosomal dominant inheritance pattern.

In mice, "lethal milk" phenotype (MIM No. 602095), a term derived from the fact that pups nursed by affected dams die before weaning, is known (25). This phenotype is caused by impaired secretion of zinc into the milk and has been shown to be the result of homozygous mutations in the *SLC30a4/Znt4* gene (25). However, there have been no reports of a similar condition in humans.

Remarks

Zinc is essential for the growth and development of infants and children. Thus, developing possible nutritional strategies to overcome zinc deficiency, in addition to zinc supplementation, would be beneficial to the health of infants and children globally. Moreover, clarification of the molecular mechanisms of AE and TNZD may give important clues to preventing premature and full-term normal infants from developing zinc deficiency, given that some countries may have an increased risk for TNZD (4). In some patients diagnosed with AE, no mutations are found in the *ZIP4/SLC39A4* gene (26), which may suggest that zinc transporters other than ZIP4 may be involved in the zinc absorption process in the small intestine.

References

1. Wardlaw T, Salama P, Brocklehurst C, Chopra M, Mason E. 2010 Diarrhoea: Why children are still dying and what can be done *Lancet* **375**, 870-872
2. Penny ME. 2013 Zinc supplementation in public health *Ann Nutr Metab* **62 Suppl 1**, 31-42
3. Moran VH, Stammers AL, Medina MW, Patel S, Dykes F, Souverein OW, Dullemeijer C, Perez-Rodrigo C, Serra-Majem L, Nissensohn M, Lowe NM. 2012 The relationship between zinc intake and serum/plasma zinc concentration in children: A systematic review and dose-response meta-analysis *Nutrients* **4**, 841-858
4. Kambe T, Hashimoto A, Fujimoto S. 2014 Current understanding of zip and znt zinc transporters in human health and diseases *Cell Mol Life Sci* **71**, 3281-3295
5. Lonnerdal B, Hoffman B, Hurley LS. 1982 Zinc and copper binding proteins in human milk *Am J Clin Nutr* **36**, 1170-1176
6. Ackland ML, Michalczyk A. 2006 Zinc deficiency and its inherited disorders -a review *Genes Nutr* **1**, 41-49
7. Kienast A, Roth B, Bossier C, Hojabri C, Hoeger PH. 2007 Zinc-deficiency dermatitis in breast-fed infants *Eur J Pediatr* **166**, 189-194
8. Aggett PJ, Atherton DJ, More J, Davey J, Delves HT, Harries JT. 1980 Symptomatic zinc deficiency in a breast-fed preterm infant *Arch Dis Child* **55**, 547-550
9. Barbarot S, Chantier E, Kuster A, Hello M, Roze JC, Blouin E, Stalder JF. 2010 Symptomatic acquired zinc deficiency in at-risk premature infants: High dose preventive supplementation is necessary *Pediatr Dermatol* **27**, 380-383
10. Iglesia I, Doets EL, Bel-Serrat S, Roman B, Hermoso M, Pena Quintana L, Garcia-Luzardo MR, Santana-Salguero B, Garcia-Santos Y, Vucic V, Andersen LF, Perez-Rodrigo C, Aranceta J, Cavelaars A, Decsi T, Serra-Majem L, Gurinovic M, Cetin I, Koletzko B, Moreno LA. 2010 Physiological and public health basis for assessing micronutrient requirements in children and adolescents. The eurreca network *Matern Child Nutr* **6 Suppl 2**, 84-99
11. Kambe T, Yamaguchi-Iwai Y, Sasaki R, Nagao M. 2004 Overview of mammalian zinc transporters *Cell Mol Life Sci* **61**, 49-68

12. Fukada T, Kambe T. 2011 Molecular and genetic features of zinc transporters in physiology and pathogenesis *Metallomics* **3**, 662-674
13. Lu M, Chai J, Fu D. 2009 Structural basis for autoregulation of the zinc transporter yiip *Nat Struct Mol Biol* **16**, 1063-1067
14. Andrews GK. 2008 Regulation and function of zip4, the acrodermatitis enteropathica gene *Biochem Soc Trans* **36**, 1242-1246
15. Maverakis E, Fung MA, Lynch PJ, Draznin M, Michael DJ, Ruben B, Fazel N. 2007 Acrodermatitis enteropathica and an overview of zinc metabolism *J Am Acad Dermatol* **56**, 116-124
16. Kury S, Dreno B, Bezieau S, Giraudet S, Kharfi M, Kamoun R, Moisan JP. 2002 Identification of slc39a4, a gene involved in acrodermatitis enteropathica *Nat Genet* **31**, 239-240.
17. Wang K, Zhou B, Kuo YM, Zemansky J, Gitschier J. 2002 A novel member of a zinc transporter family is defective in acrodermatitis enteropathica *Am J Hum Genet* **71**, 66-73.
18. Wang F, Kim BE, Dufner-Beattie J, Petris MJ, Andrews G, Eide DJ. 2004 Acrodermatitis enteropathica mutations affect transport activity, localization and zinc-responsive trafficking of the mouse zip4 zinc transporter *Hum Mol Genet* **13**, 563-571
19. Kambe T, Andrews GK. 2009 Novel proteolytic processing of the ectodomain of the zinc transporter zip4 (slc39a4) during zinc deficiency is inhibited by acrodermatitis enteropathica mutations *Mol Cell Biol* **29**, 129-139
20. Kawamura T, Ogawa Y, Nakamura Y, Nakamizo S, Ohta Y, Nakano H, Kabashima K, Katayama I, Koizumi S, Kodama T, Nakao A, Shimada S. 2012 Severe dermatitis with loss of epidermal langerhans cells in human and mouse zinc deficiency *J Clin Invest* **122**, 722-732
21. Chowanadisai W, Lonnerdal B, Kelleher SL. 2006 Identification of a mutation in slc30a2 (znt-2) in women with low milk zinc concentration that results in transient neonatal zinc deficiency *J Biol Chem* **281**, 39699-39707
22. Lasry I, Seo YA, Ityel H, Shalva N, Pode-Shakked B, Glaser F, Berman B, Berezovsky I, Goncearenco A, Klar A, Levy J, Anikster Y, Kelleher SL, Assaraf YG. 2012 A dominant negative heterozygous g87r mutation in the zinc

transporter, znt-2 (slc30a2), results in transient neonatal zinc deficiency *J Biol Chem* **287**, 29348-29361

23. Itsumura N, Inamo Y, Okazaki F, Teranishi F, Narita H, Kambe T, Kodama H. 2013 Compound heterozygous mutations in slc30a2/znt2 results in low milk zinc concentrations: A novel mechanism for zinc deficiency in a breast-fed infant *PLoS One* **8**, e64045
24. Lova Navarro M, Vera Casano A, Benito Lopez C, Fernandez Ballesteros MD, Godoy Diaz DJ, Crespo Erchiga A, Romero Brufau S. 2014 Transient neonatal zinc deficiency due to a new autosomal dominant mutation in gene slc30a2 (znt-2) *Pediatr Dermatol* **31**, 251-252
25. Huang L, Gitschier J. 1997 A novel gene involved in zinc transport is deficient in the lethal milk mouse *Nat Genet* **17**, 292-297.
26. Paul SP, Vamvakiti E, Atherton DJ, Candy DC. 2011 Acrodermatitis enteropathica variant with borderline plasma zinc concentrations *J Pediatr Gastroenterol Nutr* **52**, 630

Table 1. Zinc transporters with mutations and SNPs causing inherited diseases

Genes	Diseases	MIM No.	Clinical features
ZIP4	Acrodermatitis enteropathica (AE)	201100	Eczematous dermatitis on the perioral, perianal, and acral areas; alopecia; diarrhea; growth retardation and delay; mental slowing; poor wound healing in advanced disease Ameliorated with zinc supplementation (1-3 mg/kg/day)
ZnT2	Transient neonatal zinc deficiency (TNZD)	608118	Erythematous and erosive dermatitis around the mouth, genital region, neck, and fingers; diarrhea; hair loss Ameliorated with zinc supplementation during nursing

Figure 1. Illustrations of the predicted membrane topology of ZIP4 and ZnT2.
ZIP4 accumulates in the apical membrane of intestinal epithelial cells to facilitate the uptake of zinc from the intestinal lumen during zinc deficiency. The proteolytic cleavage (processing, see text) is thought to occur around the CPALLY motif just before the first transmembrane domain. ZIP4 is rapidly degraded by lysosomal and proteosomal pathways in zinc sufficient conditions (*left*). ZnT2 is localized in secretory vesicles in mammary epithelial cells and plays an indispensable role in the supply of zinc into breast milk. This is thought to be mediated through zinc release into the alveolar lumen (*right*). Similar topologies are predicted for other ZIP and ZnT transporters. Most ZIP and ZnT transporters have a histidine-rich loop (His-rich loop) in the cytosol.